Jpn J Ophthalmol 2009;53:18–23
DOI 10.1007/s10384-008-0617-8

CLINICAL INVESTIGATION

Effect of Travoprost on Intraocular Pressure During 12 Months of Treatment for Normal-Tension Glaucoma

Min Hee Suh[1,2], Ki Ho Park[1,2], and Dong Myung Kim[1,2]

[1] Department of Ophthalmology, Seoul National University College of Medicine, Seoul, Korea;
[2] Seoul Artificial Eye Center, Seoul National University Hospital Clinical Research Institute, Seoul, Korea

Abstract

Purpose: To evaluate the intraocular pressure (IOP)-lowering effect of travoprost in normal-tension glaucoma (NTG) over a 12-month follow-up.

Methods: Forty-five eyes of 45 patients with unilateral NTG were treated with travoprost (0.004%) once a day for 12 months. Mean IOP and the IOP reduction from baseline were assessed at 0.5, 1, 3, 6, 9, and 12 months after the initiation of the treatment. Adverse ocular event frequency and the frequency of discontinuation of treatment due to adverse events were evaluated.

Results: Mean IOP during 12 months of travoprost treatment ranged from 11.17 to 11.82 mmHg, and the mean IOP reduction in relation to baseline IOP from –2.71 to –3.71 mmHg (–18.3% to –25.1%). Mean IOP and IOP changes in the travoprost-treated and control groups were significantly different at every follow-up ($P < 0.05$ in each case). Both the magnitude ($r = 0.6992$) and percentage ($r = 0.5464$) of IOP reductions correlated positively with baseline IOP values. Ocular adverse events were usually mild to moderate and resolved without treatment.

Conclusions: Travoprost was well tolerated and significantly reduced IOP in NTG patients. In addition, initial IOP reductions were maintained throughout follow-up. Travoprost was found to be more effective in patients with greater baseline IOP. **Jpn J Ophthalmol** 2009;53:18–23 © Japanese Ophthalmological Society 2009

Key Words: adverse event, intraocular pressure, normal tension glaucoma, travoprost

Introduction

Travoprost 0.004% (Travatan, Alcon Laboratories, Fort Worth, TX, USA) is a synthetic ester prodrug of a prostaglandin F2 ($PGF_{2\alpha}$) analog with high affinity for the prostaglandin F (FP) receptor[1] and was first marketed in March 2001. Travoprost effectively reduces intraocular pressure (IOP); it is as effective as latanoprost and more effective than timolol in eyes with primary open-angle glaucoma (POAG) and ocular hypertension (OHT).[2–6]

Netland et al.[7] suggested that the response to travoprost is better than that to latanoprost or timolol in patients with IOP < 16 mmHg. As a result, it is generally believed to be effective in lowering IOP in eyes with normal-tension glaucoma (NTG) and IOP < 21 mmHg. However, to the best of our knowledge, no study has evaluated the effects of travoprost in NTG patients.

This study was undertaken to evaluate the IOP-lowering effects of travoprost in NTG patients over a 12-month period. In addition, major ocular adverse events were documented and assessed.

Patients and Methods

The study protocol was approved by the Institutional Review Board of Seoul National University Hospital. Forty-

Received: April 17, 2008 / Accepted: August 29, 2008
Correspondence and reprint requests to: Ki Ho Park, Division of Ophthalmology, College of Medicine, Seoul National University, 28 Yongon-dong, Chongno-gu, Seoul 110-744, Korea
e-mail: kihopark@snu.ac.kr

five eyes of 45 patients with unilateral NTG involvement were followed by one specialist (KHP) at the Seoul National University Hospital Glaucoma Clinic between September 2004 and September 2007. Patients were regarded as having NTG if they had glaucomatous optic-disc cupping with a glaucomatous visual field defect not attributable to another ocular or systemic pathology and an open angle on gonioscopy. In addition, affected eyes had a peak IOP < 21 mmHg (measured by Goldmann applanation tonometry of the diurnal IOP curve without medication). The patients had no previous history of ocular trauma, antiglaucoma treatment, intraocular surgery or procedure, systemic or ocular medications, or cardiac or pulmonary disease that might affect IOP. In addition, they did not have any preexisting ocular disease, such as severe inflammatory eye disease or dry eye, or a periocular cutaneous disease, that might be mistaken for an ocular adverse event. All patients enrolled in the study were instructed to apply travoprost 0.004% to the affected eye every evening.

Initial ophthalmologic exams included visual acuity (VA), refraction, IOP measurement, anterior segment evaluation, gonioscopy, and an optic disc exam with a fully dilated pupil. In addition, a visual field examination was conducted using the 30-2 program Humphrey field analyzer (HFA 30-2) (Zeiss-Humphrey Instruments, Dublin, CA, USA) before the initiation of treatment in all patients.

Two measurements of IOP by Goldmann applanation tonometry were performed with a 2-week interval prior to commencement of treatment, and baseline IOP was defined as the average of the two. Follow-up IOPs were obtained at 0.5, 1, 3, 6, 9, and 12 months after commencement of treatment. Patients who discontinued eye drops were also followed up regularly (0.5, 1, 3, 6, 9, and 12 months). Patients IOPs were measured at the same time of the day during each follow-up visit.

Ocular adverse events were determined from unsolicited patient complaints or patient-generated questions. Adverse events included conjunctival hyperemia, itching, stinging, foreign body sensation, hypertrichosis, periocular hyperpigmentation, deepening of the superior sulcus, and iris pigmentation. Subjective symptoms were included only if they could be differentiated from ordinary symptoms that predated treatment. In addition, objective signs that treated eyes differed from the contralateral control eyes were documented. To avoid interobserver variations, all examinations were performed by one specialist (KHP), and information regarding the eyes, including treatment group allocation, was masked during IOP and adverse event evaluations.

An inadequate IOP reduction was defined as an IOP reduction of less than 10% from baseline at two subsequent visits. Those patients with added or changed medications were considered to have dropped out of the study. In addition, patients were removed from the study if they refused treatment because of a travoprost application problem or were considered by the investigator to be at risk for clinically significant adverse events. If multiple complications occurred in a patient removed from the study, the most important adverse event was deemed responsible for the discontinuation. Patients lost to follow-up without definite adverse events and those who applied travoprost bilaterally were also excluded.

Statistical analysis was performed with the χ-squared test and the unpaired t test. Linear regression was used to analyze correlations between baseline IOP and magnitude and percentage of IOP reductions. Multiple regression analysis was used to identify factors that influenced IOP reductions, such as baseline IOP, age, and sex. All statistical analyses were performed with GraphPad InStat version 3.05 for Windows (GraphPad Software, San Diego, CA, USA). A P value of <0.05 was considered statistically significant.

Results

Forty-five eyes of 45 patients with NTG were enrolled. Patient characteristics are listed in Table 1. Mean baseline IOP was 14.79 ± 2.51 mmHg in travoprost-treated eyes and 14.37 ± 2.81 mmHg in contralateral control eyes, which was not significantly different. Patients were followed for at least 3 months, except for four patients who discontinued treatment owing to complications associated with treatment during the first 3 months (Fig. 1); 48.9% (22 eyes) were followed for 12 months, and 64% (29 eyes) for 9 months. Eleven patients (24.4%) were lost to follow-up: four were referred to other glaucoma clinics, five spontaneously dropped out owing to death or to the progression of an underlying disease, and the remaining two were lost to follow-up for unknown reasons (Fig. 1). In fact, only two patients discontinued treatment because of insufficient IOP control, which was noted at the 5- and 8-month follow-up visits, respectively.

Mean IOP at follow-up visits ranged from 11.17 to 11.82 mmHg (Table 2), and mean IOP reductions measured at the follow-ups ranged from –2.71 to –3.71 mmHg (–18.3% to –25.1%) relative to baseline. Significant differ-

Table 1. Patient demographic data

	Eyes (n = 45)
Age (years)	54.4 ± 12.78
Sex (male/female)	24/21
Mean follow-up period (months)	8.62 ± 3.52
Diabetes (+/–)	10/35
Hypertension (+/–)	9/36
Laterality (right/left)	22/23
Lens status (phakic/pseudophakic/aphakic)	45/0/0
VA on initial visit (logMAR)	–0.12 ± 0.22
Baseline IOP (mmHg)	14.8 ± 2.5
CCT (μm)	515.32 ± 21.34
Refractive error (diopters)	–2.29 ± 3.56
HFA 30-2	
MD (dB)	–4.09 ± 3.40
PSD (dB)	5.14 ± 3.90

Values indicate mean ± SD.

VA, visual acuity; IOP, intraocular pressure; CCT, central corneal thickness; HFA, Humphrey field analyzer; MD, mean deviation; PSD, pattern standard deviation.

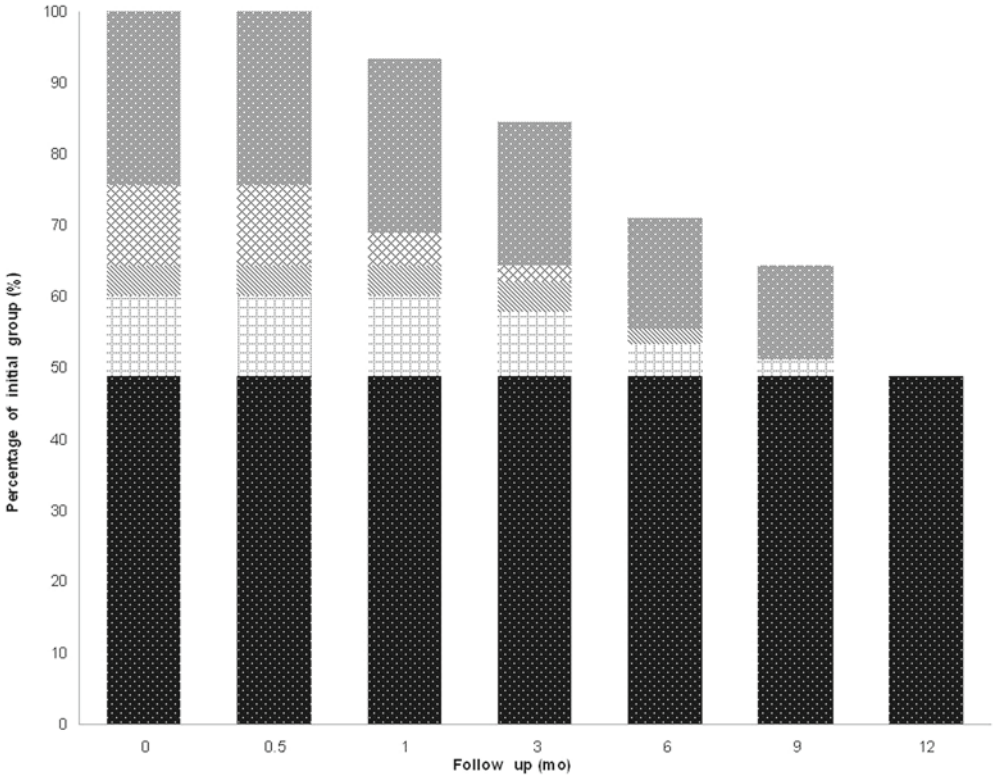

Figure 1. Distribution (expressed as percentage) of duration of follow-up for 45 patients with normal tension glaucoma (NTG). Reasons for withdrawal are demonstrated in the different column patterns.
■, Continued; ⌗, bilateral application; ▨, insufficient intraocular pressure reduction; ▩, complications; ▩, no follow-up. mo, months.

Table 2. Changes of intraocular pressure

	Travoprost-treated eye	Control eye	*P* value
IOP (mmHg)			
Baseline	14.79 ± 2.51	14.37 ± 2.81	NS
0.5 months	11.37 ± 2.04	12.93 ± 2.99	0.0086
1 months	11.30 ± 2.33	13.40 ± 2.56	<0.0001
3 months	11.40 ± 2.21	13.41 ± 2.57	<0.0001
6 months	11.42 ± 2.13	13.48 ± 2.52	<0.0001
9 months	11.35 ± 2.12	13.04 ± 2.70	0.0155
12 months	11.82 ± 2.35	13.41 ± 2.81	<0.0001
IOP change mmHg (%)			
Baseline	0	0	-
0.5 month	–3.42 ± 2.60 (–23.1)	–1.20 ± 2.55 (–8.4)	<0.0001
1 month	–3.50 ± 2.25 (–23.6)	–1.16 ± 1.66 (–8.1)	<0.0001
3 months	–3.40 ± 2.31 (–23.0)	–1.20 ± 2.08 (–8.4)	<0.0001
6 months	–3.71 ± 2.07 (–25.1)	–1.42 ± 2.06 (–10.0)	<0.0001
9 months	–3.50 ± 2.00 (–23.6)	–1.70 ± 2.40 (–11.8)	<0.0001
12 months	–2.71 ± 3.90 (–18.3)	–0.50 ± 1.91 (–3.5)	0.028

Values indicate mean ± SD.
NS, not significant.

ences were observed in mean IOP and IOP changes at all follow-up visits between travoprost-treated eyes and control eyes. The effect of travoprost was evident at the 1-month follow-up visit, and mean IOP had decreased by more than 20% at the 9-month follow-up visit. A slight increase in mean IOP was observed between 9 and 12 months, but 12-month IOPs were significantly lower than baseline IOPs (Table 2).

Forty-two percent of treated eyes (19 eyes) achieved a mean IOP reduction of at least 20%, whereas only 8.9% (four eyes) of control eyes achieved this. In addition, 15.6% of treated eyes (seven eyes) achieved an IOP reduction of at least 30%, whereas no control eye achieved this level of reduction.

The absolute and relative IOP reductions were significantly correlated with IOP at baseline ($r = 0.6992$ and $r = 0.5464$, respectively; Fig. 2). In addition, eyes with baseline IOP ≥ 15 mmHg achieved significantly greater IOP reductions at all follow-up visits than those with baseline IOP < 15 mmHg ($P = 0.0012$, 0.0057, 0.0016, 0.0133, 0.0375, and

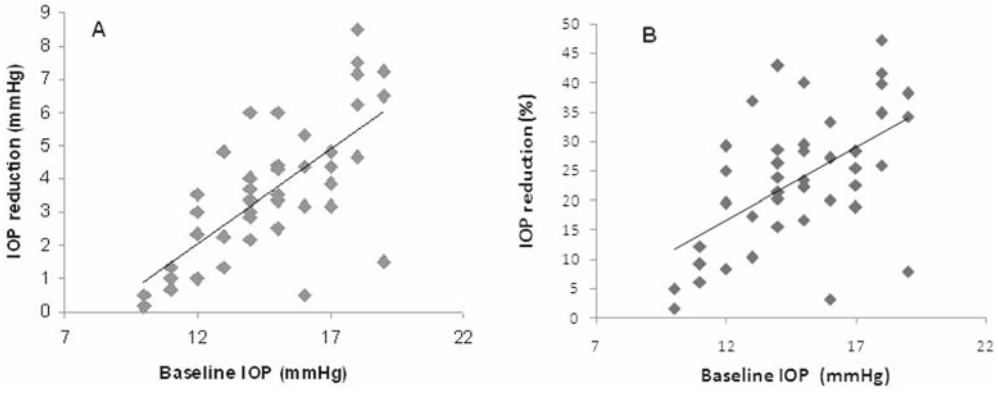

Figure 2A,B. Correlation between baseline intraocular pressure (IOP) and mean magnitude of IOP reduction (r = 0.6992, $P < 0.0001$, linear regression) (**A**), and mean percentage reduction in IOP (r = 0.5464, P = 0.0002, linear regression). (**B**) by travoprost instillation.

Table 3. Frequencies of ocular adverse events (n = 45)

Adverse events	Number of events	%
Conjunctival hyperemia	13	26.67
Itching	2	4.44
Stinging	4	8.89
Foreign body sensation	3	6.67
Hypertrichosis	4	8.89
Periocular hyperpigmentation	5	11.11
Superior sulcus deepening	3	6.67
Iris pigmentation	1	2.22

Table 4. Frequencies of treatment discontinuation for adverse events (n = 45)

Adverse event	Number of events	%
Conjunctival hyperemia	3	6.67
Stinging	1	2.22
Eyelid hyperpigmentation	1	2.22

0.042 at 0.5, 1, 3, 6, 9, and 12-month follow-ups, respectively). Multivariate logistic regression revealed that baseline IOP was most correlated with absolute and relative IOP reductions (t = 6.377, $P < 0.0001$ and t = 4.323, $P < 0.0001$, respectively).

Thirty-four ocular adverse events occurred in 23 patients (Table 3). These events were usually mild to moderate. They were either stable or improved slightly, but were not completely resolved, at the end of the study. However, the patients affected did not complain of these adverse events and medication compliance was good. The most common adverse event was conjunctival hyperemia (Table 3). Five patients (11.1%) discontinued treatment because of complications, and hyperemia was the most common cause (Table 4). However, only two patients showed clinically meaningful symptoms and signs (one with moderate hyperemia of more than grade 2,[4] and another with an intolerable stinging sensation). Four patients showed mild hyperemia (grade 0 or 1)[4] or hyperpigmentation and were discontinued for poor compliance (Table 4).

All 22 cases of hyperemia and ocular irritation symptoms, such as itching, stinging, and foreign body sensation, occurred before the 1-month follow-up. Four cases of hypertrichosis and five cases of hyperpigmentation presented at the 3- and 6- month follow-ups, respectively. However, three cases of deepening of the superior sulcus were observed at the 9- to 24-month follow-ups.

Discussion

In the present study, travoprost administered daily successfully reduced IOP in NTG patients. Travoprost treatment for 1 month effectively reduced IOP and then continued to reduce IOP values over the 12-month treatment period. The slight increase in IOP observed between 9 and 12 months was due to the loss of 6 patients to follow-up because their IOP was well controlled at 9 months (Fig. 1). To the best of our knowledge, no study has evaluated the efficacy of travoprost in NTG patients. Thus, the findings of this study expand knowledge of the therapeutic effects of travoprost in terms of IOP reduction to include NTG as well as OHT and POAG.[2–6]

In previous studies of OHT and POAG, travoprost was found to reduce IOP in the same manner as latanoprost and to be more effective than timolol.[2–6] However, no study has compared the efficacies of travoprost, latanoprost, and timolol in NTG. Tomita et al.[8] reported that latanoprost and timolol reduced IOP by 13%–15% in NTG patients, whereas in the present study, travoprost reduced IOP by 18.3%–25.1%. Ang et al.[9] reported that 41% of NTG eyes treated with latanoprost (0.005%) achieved IOP reductions of at least 20%, and that 10% of eyes achieved a reduction of at least 30%, results consistent with our findings for travoprost. Therefore, our findings suggest that in terms of IOP reduction in NTG, travoprost is as effective as, or more effective than, latanoprost and timolol. Baseline characteristics of patients such as age, sex, baseline IOP, and mean deviations of HFA 30-2 results are comparable in these three studies, but different methodologies and follow-up periods hinder direct comparison. Thus, a further prospective comparative study of the efficacies of travoprost, latanoprost, and timolol is warranted in NTG patients.

In terms of factors that influence IOP reduction, we found that baseline IOP was positively correlated with the

Jpn J Ophthalmol
Vol 53: 18–23, 2009

degree of IOP reduction (Fig. 2), indicating that, like latanoprost, travoprost has a greater IOP-lowering effect in eyes with a higher baseline IOP.[10–12]

The frequencies and types of ocular adverse events encountered during the present study are similar to those reported by previous studies.[2–5,13–15] Conjunctival hyperemia was the most common adverse event, as has been previously reported, and the frequency observed in the present study (26.67%) compares with previously reported frequencies (11.6%–58.0%).[2–5,13–15] In the present study, the frequencies of adverse ocular events, including ocular irritation symptoms and periocular changes, reached 20% and 28%, respectively, and these results also concur with those of previous reports (24.5%–41.5% and 4.7%–76% respectively).[2–5,13–15] In addition, the frequency of iris pigmentation in the present study (2.22%) also agrees with that previously reported (0%–3.6%).[2–4,15]

Five of our 45 patients (11.1%) discontinued treatment because of ocular adverse events (mainly hyperemia), which is higher than the 4.5% (9 of 202 eyes) reported by Fellman et al.[4] However, in the present study, only two of the 45 eyes (4.4%) presented clinically significant ocular signs warranting immediate discontinuation. This result concurs with the findings of previous studies, which reported that most ocular adverse events were not serious and resolved without intervention. Moreover, most of these adverse events was cosmetic in nature and thus did not present safety issues.[2–5] Further studies with longer follow-up are required to evaluate the safety of travoprost.

As has been reported by others, hyperemia and ocular irritation symptoms occurred soon after initiation of treatment (within 1 month).[4,16] On the other hand, the hyperpigmentation and hypertrichosis caused by travoprost developed earlier than those caused by latanoprost (7–15 months) and later than those caused by bimatoprost (1–2 months).[17,18] We suggest that this difference is probably due to the greater affinity travoprost has for the FP receptor than latanoprost, owing to the presence of a fluoromethylphenoxy group at carbon-17 in travoprost.[19] Unlike bimatoprost, which does not need to be converted to an active metabolite to have pharmacological activity, travoprost should be hydrolyzed by corneal esterase to a free fatty acid to activate the FP receptor. This accounts for the slower onset of adverse events observed after travoprost application.[18,19]

Interestingly, a deepening of the superior sulcus was observed in three cases including two that have been recently reported (Fig. 3).[20] There has been only one case report suggesting that bimatoprost induces deepening of the superior sulcus.[21] This complication occurred more gradually than did other periocular changes, such as hyperpigmentation or hypertrichosis.

It should be noted that the present study was inherently limited by its retrospective nature and by the small number of patients recruited. In addition, follow-up IOP values were measured at only one time of day, and ocular adverse events were not graded in all eyes. Nevertheless, we were able to exclude important confounding factors, such as age, sex, and follow-up period, by adopting an intraindividual comparison model.

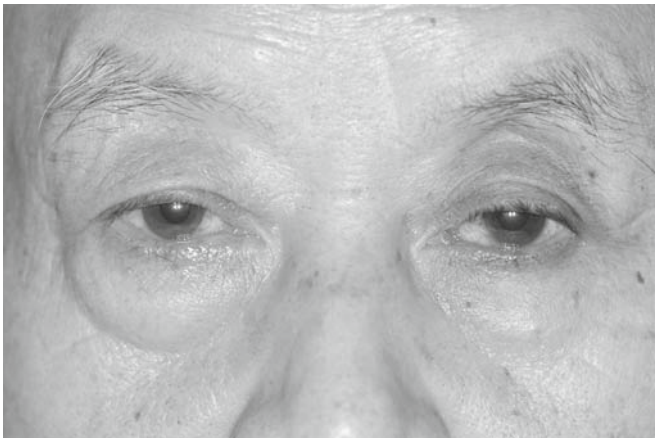

Figure 3. Deepening of the superior sulcus and hyperpigmentation of the left eye were noticed in this patient 2 years after treatment with travoprost 0.004%.[20]

In conclusion, travoprost was found to be well tolerated and to significantly reduce IOP in NTG patients, and initial IOP reductions, substantively achieved at 1 month, were maintained throughout the 12-month follow-up period. Furthermore, travoprost was found to be more effective in patients with a higher baseline IOP.

References

1. Hellberg MR, Sallee VL, McLaughlin MA, et al. Preclinical efficacy of travoprost, a potent and selective FP prostaglandin receptor agonist. J Ocul Pharmacol Ther 2001;17:421–432.
2. Netland PA, Landry T, Sullivan EK, et al. Travoprost compared with latanoprost and timolol in patients with open-angle glaucoma or ocular hypertension. Am J Ophthalmol 2001;132:472–484.
3. Goldberg I, Cunha-Vaz J, Jakobsen JE, et al. Comparison of topical travoprost eye drops given once daily and timolol 0.5% given twice daily in patients with open-angle glaucoma or ocular hypertension. J Glaucoma 2001;10:414–422.
4. Fellman RL, Sullivan EK, Ratliff M, et al. Comparison of travoprost 0.0015% and 0.004% with timolol 0.5% in patients with elevated intraocular pressure: a 6-month, masked, multicenter trial. Ophthalmology 2002;109:998–1008.
5. Barnebey HS, Orengo-Nania S, Flowers BE, et al. The safety and efficacy of travoprost 0.004%/timolol 0.5% fixed combination ophthalmic solution. Am J Ophthalmol 2005;140:1–7.
6. Hoyng PF, Kitazawa Y. Medical treatment of normal tension glaucoma. Surv Ophthalmol. 2002;47 Suppl 1:116S–124S.
7. Netland PA, Robertson SM, Sullivan EK, et al. Response to travoprost in black and nonblack patients with open-angle glaucoma ocular hypertension. Adv Ther 2003;20:149–163.
8. Tomita G, Araie M, Kitazawa Y, Tsukahara S. A three-year prospective, randomized and open comparison between latanoprost and timolol in Japanese normal-tension glaucoma patients. Eye 2004;18:984–989.
9. Ang A, Reddy MA, Shepstone L, Broadway DC. Long term effect of latanoprost on intraocular pressure in normal tension glaucoma. Br J Ophthalmol 2004;88:630–634.
10. Oh JY, Park KH. The effect of latanoprost on intraocular pressure during 12 months of treatment for normal-tension glaucoma. Korean J Ophthalmol 2005;19:297–301.

11. Tamada Y, Taniguchi T, Murase H, et al. Intraocular pressure-lowering efficacy of latanoprost in patients with normal-tension glaucoma or primary open-angle glaucoma. J Ocul Pharmacol Ther 2001;17:19–25.
12. Rulo AH, Greve EL, Geijssen HC, Hoyng PF. Reduction of intraocular pressure with treatment of latanoprost once daily in patients with normal pressure glaucoma. Ophthalmology 1996;103:1276–1282.
13. Konstas AG, Kozobolis VP, Katsimpris IE, et al. Efficacy and safety of latanoprost versus travoprost in exfoliative glaucoma patients. Ophthalmology 2007;114:653–657.
14. Parrish RK, Palmberg P, Sheu WP, et al. A comparison of latanoprost, bimatoprost, and travoprost in patients with elevated intraocular pressure: a 12-week, randomized, masked-evaluator multicenter study. Am J Ophthalmol 2003;135:688–703.
15. Orengo-Nania S, Landry T, Von Tress M, et al. Evaluation of travoprost as adjunctive therapy in patients with uncontrolled intraocular pressure while using timolol 0.5%. Am J Ophthalmol 2001;132:860–868.
16. Camras CB and the United States Latanoprost Study Group. Comparison of latanoprost and timolol in patients with ocular hypertension and glaucoma: a six-month, masked, multicenter trial in the United States. Ophthalmology 1996;103:138–147.
17. Kook MS, Lee K. Increased eyelid pigmentation associated with use of latanoprost. Am J Ophthalmol 2000;129:804–806.
18. Tosti A, Pazzaglia M, Voudouris S, Tosti G. Hypertrichosis of the eyelashes caused by bimatoprost. J Am Acad Dermatol 2004;51:1040.
19. Woodward DF, Krauss P, Chen J, et al. The pharmacology of bimatoprost (Lumigan). Surv Ophthalmol 2001;45 Suppl 4:337S–345S.
20. Yang HK, Park KH, Kim TW, Kim DM. Eyelid superior sulcus deepening after topical travoprost treatment. Jpn J Ophthalmol 2009; in press.
21. Peplinski LS, Albiani SK. Deepening of lid sulcus from topical bimatoprost therapy Optom Vis Sci 2004;81:574–577.